Acta Poloniae Pharmaceutica – Drug Research, Vol. 72 No. 3 pp. 539–549, 2015 ISSN 0001-6837
Polish Pharmaceutical Society

EVALUATION OF SORPTIVE PROPERTIES OF VARIOUS CARRIERS AND COATING MATERIALS FOR LIQUISOLID SYSTEMS

BARBORA VRANÍKOVÁ and JAN GAJDZIOK*

Department of Pharmaceutics, Faculty of Pharmacy, University of Veterinary and Pharmaceutical Sciences, Palackého 1/3, Brno 612 42, Czech Republic

Abstract: The basic principle of liquisolid systems formulation lies in the conversion of the drug in a liquid state into an apparently dry, free-flowing and readily compressible powder by its blending (or spraying) with specific carriers and coating materials. The selection of the most suitable carrier and coating material depends especially on their values of flowable liquid retention potential (Φ), which is defined as the maximum mass of liquid that can be retained per unit mass of powder material, while maintaining an acceptable flowability. The presented work focused on the determination of the maximum amount of propylene glycol (PG), which can be retained by several selected carriers and coating materials while maintaining acceptable flow properties of the liquisolid powder blend. Granulated forms of magnesium aluminometasilicates (Neusilin® US2 and Neusilin® NS2N), dibasic calcium phosphate (Fujicalin®) and microcrystalline cellulose (Avicel® PH 101) were tested due to their frequent use. Powdered forms of magnesium aluminometasilicate (Neusilin® UFL2) and colloidal silica (Aerosil® 200) were used as common coating materials. From the evaluation of liquisolid mixtures with different amounts of liquid, it could be observed that 1 g of Neusilin® US2, Neusilin® UFL2, Neusilin® NS2N, Aerosil® 200, Fujicalin® and Avicel® PH 101 can retain 1.00, 0.97, 0.54, 0.04, 0.25 and 0.12 g of propylene glycol, respectively, while maintaining acceptable flowing properties for further processing.

Keywords: liquisolid systems, flowable liquid retention potential, carrier, coating material, aluminometasilicates, microcrystalline cellulose, Aerosil®, Neusilin®, Fujicalin®

Liquisolid systems (LSS) formulation represents a new, innovative and promising method in the production of solid dosage forms with enhanced *in vitro* dissolution rate and improved *in vivo* bioavailability of poorly soluble drugs. The basic principle of LSS formulation lies in sorption of a drug in liquid state onto specific carriers and coating materials, resulting in formation of apparently dry, free-flowing and readily compressible powder (1). The active ingredients are in liquisolid systems in a similar state as in soft gelatin capsules filled by a liquid drug (non-volatile liquid vehicle is used to dissolve the solid drug and the final preparation does not involve drying or evaporation process) (2). It is well established that these formulations show higher and more consistent bioavailability than conventional oral dosage forms because the active ingredient is already dissolved.

Properties of carriers, such as specific surface area (SSA) and liquid absorption capacity, are the most important factors in the formulation of liquisolid systems because they allow incorporation of a greater amount of the drug in liquid state (3, 4). Therefore, the selection of a carrier mainly depends on its specific surface area, liquid adsorption capacity, flowability and compressibility (5).

In the past, *colloidal silica* (SSA – 200 m^2/g) (6) was used as a carrier material to prepare the predecessors of liquisolid systems called "Powdered Solutions". However, these preparations did not have suitable properties facilitating their compression into tablets (5). Compression enhancers such as microcrystalline cellulose were added to powdered solutions to increase the compressibility of the formulation. Nevertheless, product properties were never standardized to comply with industrial requirements (7). In modern liquisolid system formulations, colloidal silica is used as a coating material absorbing the excessive liquid from the carrier and thus ensuring good flowability of the created admixture (8).

To date, the most commonly used carrier in LSS has been the microcrystalline cellulose (MCC) with SSA about 1.18 m^2/g (9). It has been used to

* Corresponding author: e-mail: gajdziokj@vfu.cz; phone: +420 541562869; fax: +420 549240589

prepare liquisolid tablets containing bromhexine hydrochloride (10), ezetimibe (11), flutamide (12), nifedipine (13), valsartan (14), etc. A frequent use of MCC in liquisolid system formulation is caused by its long-term utilization in pharmaceutical industry, low price, good stability and availability in different particle sizes and moisture grades (15). Moreover, in previous studies it was shown that carriers other than MCC, e.g., lactose (SSA – 0.35 m^2/g) (9), sorbitol (SSA – 0.37 m^2/g) (9) and starch (SSA – 0.60 m^2/g) (9), were required in higher amounts for the conversion of a drug in liquid state into dry, non-adherent and free-flowing powdered form (16). This was attributed to a higher specific surface area of MCC (16). However, on the market, there are available several substances with extremely large SSA and significantly higher liquid absorption capacity, such as magnesium aluminometasilicates, anhydrous dibasic calcium phosphate, mesoporous silicates, etc. (17, 18).

The first of them Fujicalin® is a synthetic spherically agglomerated anhydrous dibasic calcium phosphate. The unique production process of Fujicalin® consists of a restricted crystal growth of anhydrous dibasic calcium phosphate followed by spray drying of aqueous dispersion of these microcrystals. Thereby, porous spherical particles containing microcrystals of anhydrous dicalcium phosphate are obtained (19). Its high specific surface area (40 m^2/g), porosity and ability to adsorb up to 1.2 mL/g (17) of liquid while remaining the dry, free flowing and compressible powder makes Fujicalin® a suitable carrier for liquisolid system preparations. This fact was proved by Hentzschel et al. (3), who used Fujicalin® to prepare LSS containing tocopherol acetate as a model drug.

Neusilin®, an amorphous form of magnesium aluminometasilicate, is commercially available in 11 various grades, which differ in their forms (powder, granules), bulk densities, water content, particle sizes and pHs (neutral, alkaline) (20). The application of synthetic magnesium aluminometasilicates has been an objective of several studies. Their absorption properties were used in tobacco industry, for example, where they were added to cigarette filters as aldehyde sorbents (especially formaldehyde) (21). In pharmaceutical technology, they have been used as carriers for solid dispersions to improve the drug dissolution or to granulate oily formulations and to increase the formulation stability (22). Based on its use as an excipient in various formulations, up to 1.05 g Neusilin® can be used in oral formulations per day (23). Moreover, alkaline grades of Neusilin® are approved as antacid active ingredients with a maximum dosage of 4 g/day (23). In liquisolid systems, Neusilins® can be used as carriers (granulated form) and also as coating materials (powdered form). Neusilins® are able to retain a greater amount of a drug in its liquid state than MCC. Disintegration of tablets containing Neusilin® as a carrier is slower because of its poor disintegration properties (24). Recently, Neusilin® US2 represents the most commonly used carrier for LSS formulations from the group of magnesium aluminometasilicates (3, 24). It is prepared by spray drying and thus provides a high porosity, very large SSA (up to 300 m^2/g), high liquid adsorption capacity (up to 3.4 mL/g), and anticaking and flow enhancing properties (20, 25).

Mesoporous silicates were originally developed to be applied as molecular sieves (26). In pharmaceutical technology, they were initially used for the controlled drug delivery (27-29). According to their extremely large specific surface area (up to 1500 m^2/g), large pore size and pore volume (30), ordered mesoporous silicates show a high potential in the preparation of liquisolid systems. Chen et al. (31) used hollow mesoporous silicas (HMS) as carriers for an insoluble drug carbamazepine dissolved in PEG 400. A significant improvement of the drug loading and dissolution rate demonstrated that HMS could form good reservoirs for drug solutions to enhance the dissolution of poorly water-soluble drugs (31).

This work is focused on the determination of capability of several selected carriers and coating materials to absorb propylene glycol by determining their flowable liquid retention potential for this solvent. A granulated form of magnesium aluminometasilicates (Neusilin® US2, Neusilin® NS2N), dibasic calcium phosphate (Fujicalin®) and microcrystalline cellulose (Avicel® PH 101) were used as carrier materials. A powdered form of magnesium aluminometasilicate (Neusilin® UFL2) and colloidal silica (Aerosil® 200) were used as coating materials. Different amounts of propylene glycol were added to carriers/coating materials and flow properties of liquisolid mixtures were evaluated. The flowable liquid retention potential was calculated as a liquid/solid mass ratio of the blend with angle of slide corresponding to 33˚ (4, 32).

MATERIALS AND METHODS

Materials

Magnesium aluminometasilicates (Neusilin® US2, Neusilin® NS2N and Neusilin® UFL2) and anhydrous dibasic calcium phosphate (Fujicalin®) were kindly gifted by Fuji Chemical Industry Co.,

Ltd (Japan). Avicel® PH 101 (FMC Biopolymer, Ireland) and Aerosil® 200 (Eurošarm spol. s.r.o., Czech Republic) were selected as the most commonly used carrier and coating materials. Propylene glycol (Dr. Kulich Pharma, Czech Republic) was used as non-volatile biocompatible solvent with good dissolving properties for many drugs.

Methods

Preparation of liquisolid powders

Liquisolid powders were prepared by a simple blending of carriers/coating materials with propylene glycol. The initial amount of carrier/coating material was selected based on scientific literature according to its characteristics such as specific surface area and adsorption capacity (Table 1). The carrier/coating material was mixed with the liquid vehicle using a mortar and pestle, sieved through the sieve with 1 mm mesh size and subsequently homogenized in a three-axial homogenizer (T2C, TURBULA System Schatr, Switzerland) for 10 min.

The next experimental step was adding of a liquid (usually in amount of 1 g; 0.5 g in the case of Aerosil® 200). The first two addings of PG to Neusilin® UFL2 were 2.5 g, because of the high value of angle of slide (more than 40°). After the evaluation of flow properties and angle of slide, a further amount of a liquid vehicle was added. The whole blend was sieved and homogenized again after each adding of PG. When the value of angle of slide approached 33° (considered as an optimum) (4, 32), at least two more addings of 1 g (0.5 g in case of Aerosil® 200) of propylene glycol were performed.

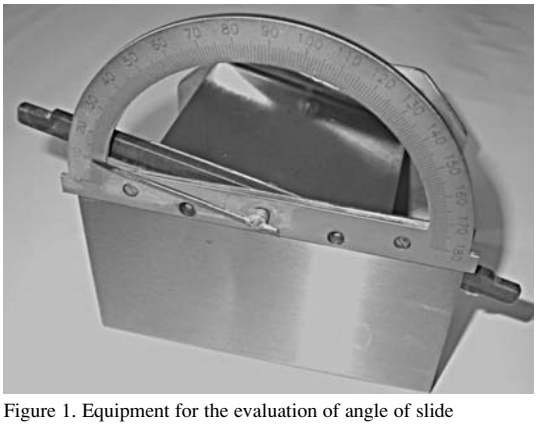

Figure 1. Equipment for the evaluation of angle of slide

Evaluation of angle of slide

Angle of slide is a specific parameter for evaluation of flow behavior of liquisolid mixtures. Spireas et al. (33) suggested that angle of slide is a preferred method to evaluate the flowability of powders with particles smaller than 150 μm.

Angle of slide was used to evaluate the flow properties of carriers/coating materials and liquisolid mixtures. The tested sample (10 g) was placed on one end of a stainless steel plate with a polished surface (Fig. 1). This end was gradually raised until the plate with the horizontal surface formed an angle at which the sample was about to slide. Three determinations were carried out; average and standard deviation were calculated. Angle of slide corresponding to 33° is regarded as optimal (32, 4).

Evaluation of angle of repose

A fixed funnel and a free-standing cone were used to measure the angle of repose. To the funnel (105 mm in diameter, 190 mm high with 105 mm long stem and internal diameter of 5 mm) was introduced 50 g (25 g in case of Aerosil® 200) of the powder mixture. Height (h) and diameter (d) of the cone of powder, which formed after the mixture flew through the funnel, were evaluated and angle of repose (α) was calculated (34). The evaluation was repeated 3 times; average and standard deviation were calculated.

Table 1. Characterizations of carriers/coating materials and their amounts used to prepare liquisolid powders.

Carrier	SSA [m^2/g]	Adsorption capacity [mL/g]	Used amount [g]	Initial amount of PG [g]
Neusilin® US2	300.0 (18)	3.4 (18)	25.0	25.0
Neusilin® UFL2	300.0 (18)	3.4 (18)	30.0	20.0
Neusilin® NS2N	250.0 (18)	2.4 (18)	35.0	15.0
Aerosil® 200	200.0 (6)	2.0 (20)	24.0	1.0
Fujicalin®	40.0 (17)	1.2 (17)	40.0	10.0
Avicel® PH 101	1.1 (9)	1.0 (20)	49.0	1.0

Evaluation of flowability (flow through the orifice)

The total of 50 g (25 g in the case of Aerosil® 200) of the tested powder sample without compacting was introduced into a dry stainless steel funnel with a closed bottom opening (diameter 25 mm) (MEDIPO, Czech Republic according to Eur. Ph.). The bottom opening of the funnel was unblocked and the time the entire sample needed to flow out of the funnel was measured. Three measurements were carried out; average and standard deviation were calculated.

Tapped and bulk density measurements

A required amount of the liquisolid powder was introduced into a dry calibrated cylinder without compacting. The powder was carefully leveled and unsettled apparent volume V_0 was recorded. Bulk density was calculated in compliance with Ph. Eur. 8 (34).

The cylinder was fixed to the base (SVM 102, ERWEKA GmbH, Germany). After 10, 500 and 1250 taps the corresponding volumes V_{10}, V_{500} and V_{1250} were marked. Tapped volumes were used to calculate the tapped density, compressibility index (CI) and Hausner ratio (HR) (34).

Determination of the flowable liquid retention potential (Φ-value)

Carrier/coating material (amount shown in Tab. 1) was mixed with varying amount of propylene glycol, sieved through the sieve with mesh size 1 mm and homogenized in three-axial homogenizer for 10 min. Thereafter, flow properties of these liquisolid mixtures were evaluated. The liquid/solid mass ratio (m/m) of blends with angle of slide corresponding to 33° was regarded as the Φ-value (Equation 1) of the excipient.

$$\Phi = \frac{m_{max}}{Q} \qquad (1)$$

where m_{max} is the maximum amount of liquid that can be retained per unit mass of the powder material (Q) while maintaining acceptable flowability.

RESULTS AND DISCUSSION

Experimental part of the presented work aimed at the determination of the maximum amount of propylene glycol (PG), which can be retained by several selected carriers and coating materials while maintaining acceptable flow properties of the liquisolid powder blend. Granulated form of magnesium aluminometasilicates (Neusilin® US2 and Neusilin® NS2N), dibasic calcium phosphate (Fujicalin®) and microcrystalline cellulose (Avicel® PH 101) were used as carrier materials. A powdered form of magnesium aluminometasilicate (Neusilin® UFL2) and colloidal silica (Aerosil® 200) were evaluated as coating materials. According to the scientific literature dealing with liquisolid systems (2, 35), angle of slide was selected as the main parameter determining flow properties of liquisolid powders. Liquisolid blends with angle of slide close to 33° were used to calculate the liquid retention potential (Φ-value, equation 1). In the case when more similar values of angle of slide close to 33° were obtained for different mixtures with various amounts of propylene glycol, other parameters, such as angle of repose, flowability, compressibility index (CI) and Hausner ratio (HR) were taken under consideration as auxiliary evaluation parameters.

Evaluation of blank carriers and coating materials

The evaluation of Neusilin® US2 flow properties (Table 2) implied that experimentally measured values of angle of slide (35.67 ± 0.58°) were higher than the required angle of 33° (32, 36). The values of angle of repose of 29.66 ± 0.92° were similar to the value presented by the manufacturer (30.00°)

Table 2. Flow properties of carriers/coating materials.

Carrier/coating material	Angle of slide [°]	SD	Angle of repose [°]	SD	Flowability [s/50 g]	SD	CI [%]	HR
Neusilin® US2	35.67	0.58	29.66	0.92	6.21	0.45	10.59	1.11
Neusilin® NFL2	39.33	0.58	41.47	0.67	75.16	3.18	24.75	1.33
Neusilin® NS2N	37.17	0.76	25.87	0.49	7.30	2.19	13.27	1.15
Aerosil® 200	47.00	2.00	NA	NA	8	NA	25.00	1.33
Fujicalin®	23.33	0.76	25.77	0.46	1.16	0.04	6.67	1.07
Avicel® PH 101	48.43	1.53	36.25	0.39	**8**	NA	24.21	1.32

NA = not available.

(20) and indicated excellent flow properties. Other parameters, e.g., compressibility index (10.59%), Hausner ratio (1.11) and flowability (6.21 ± 0.45 s/50 g) referred to its acceptable flow character (34). From Table 2 it is clear that Neusilin® UFL2 showed, due to its powder form, worse characteristics of flow in comparison to granulated forms of aluminometasilicates (Neusilin® US2 and Neusilin® NS2N). This phenomenon is well established also for other excipients (e.g., lactose, calcium sulfate, mannitol, etc.) (37, 38). Blank Neusilin® UFL2 (Neusilin® UFL2 without propylene glycol) also showed higher values of angle of slide (39.33 ± 0.58°) than optimal 33°. Experimentally measured values of angle of repose (41.47 ± 0.67°) were lower than the angle presented by the manufacturer (45.00°) (18) and values of flowability (75.16 ± 3.18 s/50 g), CI (24.75%) and HR (1.33) indicated passable flow properties of this material (34).

Neusilin® NS2N also showed higher values of angle of slide (37.17 ± 0.76°) in comparison to the recommended value of 33°. However other parameters (Table 2), such as angle of repose (25.87 ± 0.49°), flowability (7.30 ± 2.19 s/50 g), CI (13.27%) and HR (1.15) implied its excellent/good character of flow (34).

It was not possible to measure angle of repose and flowability of Aerosil® 200 because of its adhesion to the surface of funnels and cohesion of porous lightweight particles. CI = 25.00% and HR = 1.33 indicated passable flow properties of Aerosil® 200 (34). Angle of slide was 47.00 ± 2.00°, i.e., the second highest value obtained among the tested materials (Table 2).

Evaluation of flow properties of Fujicalin® implied its excellent character of flow (Table 2). Experimentally measured values of angle of repose (25.77 ± 0.46°) and compressibility index (6.67%) were lower than values presented by the manufacturer (29.50° and 15.10%) (17). Fujicalin®, due to its agglomerated character (spray drying preparation), also showed excellent flowability (1.16 ± 0.04) and low value of angle of slide (23.33 ± 0.76°).

Among the selected carriers/coating materials, Avicel® PH 101 showed the highest value of angle of slide (48.43 ± 1.53°). Experimentally measured values of angle of repose (36.25 ± 0.39°) were similar to the value given by Nada et al. (38.00) (39). Flowability of this type of MCC could not be measured and values of CI (24.21%) and HR (1.32) corresponded to passable character of flow (34).

Mixture of Neusilin® US2 with propylene glycol

From Figure 2 it could be observed that the increasing amount of propylene glycol decreased angle of slide of Neusilin® US2/PG mixtures. The blend containing 25 g of PG had the value of angle of slide closest to 33° (32.83 ± 0.29°). Other parameters of this liquisolid blend, such as angle of repose (24.63 ± 2.14°), flowability (2.57 ± 0.26 s/50 g), CI (10.20%) and HR (1.11) also complied with requirements for powders with excellent flow properties (Table 3).

From the evaluation of flow properties it is obvious that the increasing amount of propylene glycol deteriorated angle of repose and flowability of liquisolid blend (Table 3). The results implied that adding of liquid initially decreased values of angle of repose from 24.63 ± 0.00° (25 g PG) to 22.50 ± 0.00 (26 g PG). However, subsequent adding of propylene glycol increased its values up to 29.70 ± 1.78° (blend with 29 g of PG).

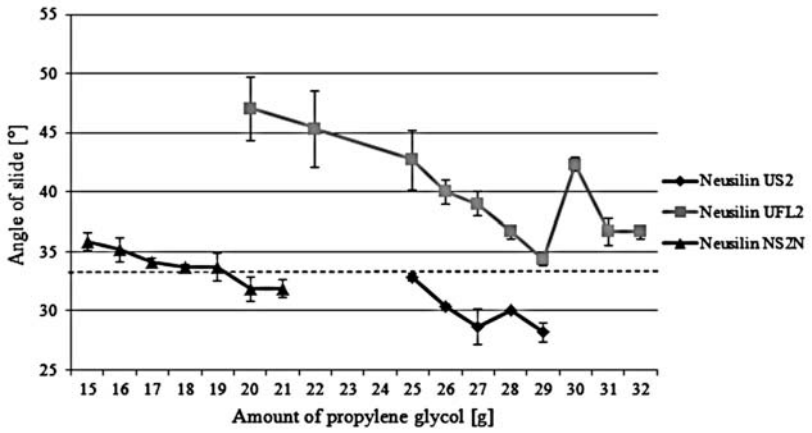

Figure 2. Angle of slide of Neusilins® /PG mixtures. The dashed line indicates the desired angle of slide 33°

Table 3. Flow properties of Neusilin® US2 and PG mixtures.

Amount of PG		Angle of repose	SD	Flowability	SD	CI	HR
[g]	[%]**	[°]		[s/50 g]		[%]	
25	**100**	**24.63**	**2.14**	**2.57**	**0.26**	**10.20**	**1.11**
26	104	22.50	0.00	2.86	0.27	9.38	1.10
27	108	24.47	0.46	3.43	0.54	12.50	1.14
28	112	26.85	0.13	3.30	0.26	13.83	1.16
29	116	29.70	1.78	3.86	0.04	14.13	1.16

* Sample with most suitable properties is written **in bold**. ** In relation to the carrier material.

Table 4. Flow properties of Neusilin® UFL2 and PG mixtures.

Amount of PG		Angle of repose	SD	Flowability	SD	CI	HR
[g]	[%]**	[°]		[s/50 g]		[%]	
20.0	66.7	41.17	0.45	8	NA	23.76	1.31
22.5	75.0	42.70	0.98	8	NA	27.55	1.38
25.0	83.3	43.53	0.29	8	NA	27.08	1.37
26.0	86.7	44.47	0.29	8	NA	26.04	1.35
27.0	90.0	42.03	0.29	8	NA	25.53	1.34
28.0	93.3	36.77	0.64	8	NA	22.89	1.30
29.0	**96.7**	**42.70**	**0.50**	8	**NA**	**25.56**	**1.34**
30.0	100.0	38.67	0.65	8	NA	19.10	1.24
31.0	103.3	34.80	0.70	8	NA	20.88	1.26
32.0	106.7	38.67	0.65	8	NA	22.45	1.29

* Sample with most suitable properties is written **in bold**. ** In relation to the coating material. NA = not available.

The flowability of liquisolid mixture of Neusilin® US2 and PG (maximum value of 3.86 ± 0.04 s/50 g in sample with 29 g of sorbed PG) was enhanced in comparison to flowability of blank Neusilin® US2 (6.21 ± 0.45 s/50 g). As can be observed from Table 3, values of flowability increased from 2.57 ± 0.26 s/50 g (mixture with 25 g of PG) to 3.86 ± 0.04 s/50 g (mixture containing 29 g of PG). This deterioration of powder flow properties could be explained by the oversaturation of carrier with higher amounts of sorbed liquid vehicle.

Compressibility index and Hausner ratio (Table 3) implied the same tendency as angle of repose (Table 3). Initially the values decreased but after adding more PG they increased again. The values correspond to powders with good/excellent flow properties (34).

The flowable liquid retention potential (Φ-value) of Neusilin® US2 mixed with PG was calculated (Equation 1) as the ratio of amount of liquid vehicle (25 g) and weight of carrier (25 g) and is equal to 1.00 (Fig. 3). This experimentally measured Φ-value is four times higher than that given by Shah et al. (40). In their study, angle of repose was used as the main parameter for the evaluation of powder flow properties, which could have caused the significant differences between values of flowable liquid retention potential (40).

Mixture of Neusilin® UFL2 with propylene glycol

Adding of 20 g of PG to Neusilin® UFL2 increased the angle of slide from 39.33 ± 0.58° to 47.00 ± 2.65°. The subsequent adding of propylene glycol decreased the mixture values to 34.33 ± 0.58° (29 g of PG), as shown in Figure 2. However, further additions of liquid vehicle increased the values of angle of slide again. Mixture containing 29 g of PG showed angle of slide 34.33 ± 0.58°, which was the closest value to 33°, regarded as optimum. Other parameters of this liquisolid powder sample, such as angle of repose (47.70 ± 0.50°), CI (25.56) and HR (1.34) referred to passable or poor character of flow (34) (Table 4).

Based on the evaluation of angle of repose, compressibility index and Hausner ratio (Table 4),

there was observed no obvious dependence on the amount of propylene glycol added to Neusilin® UFL2. All the measured values were in the range given by Ph. Eur. 8.0 for fair, passable or poor powder flow properties. The flowability of PG/Neusilin® UFL2 mixtures could not be evaluated. The insufficient character of flow is caused by the presence of Neusilin® UFL2 in its powdered form (18).

The Φ-value for the Neusilin® UFL2 mixed with PG was calculated as the ratio between the amount of liquid vehicle (29 g) and weight of carrier (30 g) and was equal to 0.97 (Fig. 3).

Mixture of Neusilin® NS2N with propylene glycol

From Figure 2 it is clear that the angle of slide decreased with the increasing amount of propylene glycol in PG/Neusilin® NS2N mixtures. The mixture containing 19 g of PG showed the value of angle of slide (33.67 ± 1.16°) closest to 33°. The mixtures' angle of repose (35.99 ± 2.05°) referred to fair flow properties and values of CI (21.28%) and HR (1.27) implied passable character of powder flow (34).

Evaluation of flow properties implied that the increasing amount of propylene glycol deteriorated angle of repose, flowability, CI and HR of liquisolid blend (Table 5).

The flowable liquid retention potential was calculated for the mixture containing 19 g of propylene glycol. The Φ-value for Neusilin NS2N is equal to 0.54 (Fig. 3).

Mixture of Aerosil® 200 with propylene glycol

Figure 4 and Table 6 imply that mixing of Aerosil 200 with propylene glycol improved flow properties of liquisolid mixtures. Values of angle of slide decreased after adding 2 g of PG to 29.00 ±

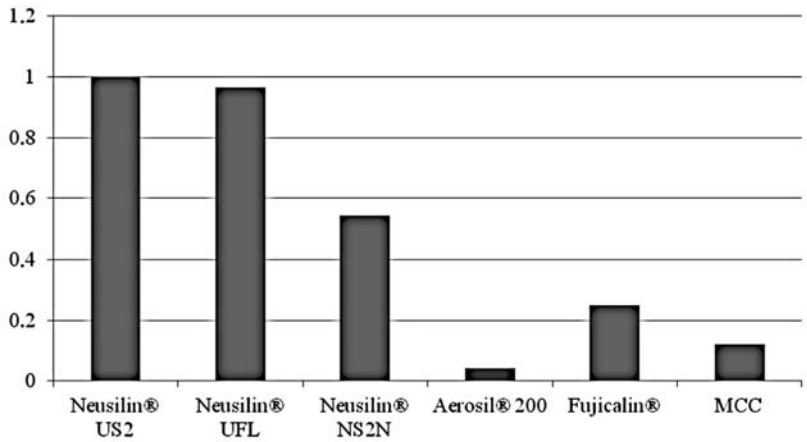

Figure 3. Flowable liquid retention potential (Φ-value) of carriers/coating materials

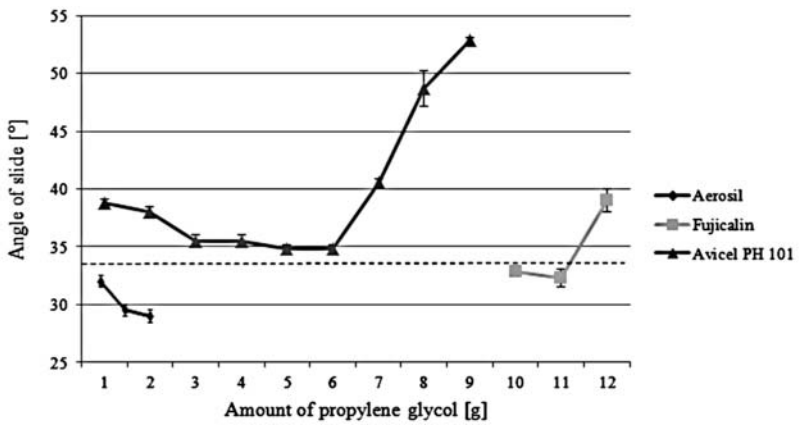

Figure 4. Angle of slide of Aerosil® 200, Fujicalin® and Avicel® PH 101 mixtures with PG. The dashed line indicates the desired angle of slide 33°

0.50°. Mixture containing 1 g of PG revealed the closest value (32.00 ± 0.50°) to the optimal angle of slide of 33°. Other parameters, such as CI (15.29%) and HR (1.18) referred to powders with good character of flow (34).

Angle of repose could not be evaluated. Flowability (Table 6) of liquisolid blends was improved by adding of propylene glycol. Polyethylene glycol could act as a lubricant (41) and hence enhance flowability of powder samples.

Values of CI and HR (Table 6) increased with the increasing amount of PG. Additions of PG caused deterioration of its flow properties from good to fair character of flow.

The Φ-value for the Aerosil® 200 mixed with PG was calculated as the ratio of amount of liquid vehicle (1 g) and weight of carrier (24 g) and is equal to 0.042 (Fig. 3). This experimentally measured value is significantly lower than values described in literature (1.5 (42) and 3.31 (43)). This difference could have been caused by poor homogeneity of the liquisolid blend prepared by simple blending. Higher homogeneity of mixtures could be reached by spraying propylene glycol onto carrier/coating material in the fluid bed equipment.

Mixture of Fujicalin® with propylene glycol

Evaluation of angle of slide (Fig. 4) implied that adding of propylene glycol increased its values in comparison to angle of slide of blank Fujicalin®. Mixture containing 10 g of PG had the closest value of angle of slide (32.83 ± 0.29°) to the recommended 33°. The angle of repose (29.70 ± 2.97°), flowability (1.03 ± 0.09 s/50 g), CI (8.24%) and HR (1.09) of this liquisolid powder sample also met the requirements for powders with excellent flow properties.

Adding of propylene glycol also had a negative effect on values of angle of repose (Table 7). The measured values increased up to 32.60 ± 1.39° (mixture containing 12 g of PG). The lowest angle of repose (27.30 ± 1.21°) had the liquisolid blend with 11 g of PG.

Evaluation of flowability (Table 7) implied that mixing of Fujicalin® with a liquid vehicle decreased its values. The flowability enhancing could be caused by filling of irregularities on carriers' surface with propylene glycol (44).

Values of CI and HR (Table 7) increased after adding PG. However, all values were in the range given by Ph. Eur. 8.0 for excellent character of powder flow.

Table 5. Flow properties Neusilin® NS2N and PG mixtures.

Amount of PG		Angle of repose	SD	Flowability	SD	CI	HR
[g]	[%]**	[°]		[s/50 g]		[%]	
15	42.9	28.61	0.81	9.31	0.55	16.49	1.20
16	45.7	31.97	0.87	10.65	0.69	16.84	1.20
17	48.6	33.91	1.44	12.34	0.31	20.00	1.25
18	51.4	36.38	3.40	11.40	0.44	20.21	1.25
19	**54.3**	**35.99**	**2.05**	**10.37**	**0.24**	**21.28**	**1.27**
20	57.1	35.34	070	9.48	0.27	22.58	1.29
21	60.0	40.11	0.71	8.12	0.96	21.11	1.27

* Sample with most suitable properties is written **in bold**. ** In relation to the carrier material.

Table 6. Flow properties of Aerosil® 200 and PG mixtures.

Amount of PG		Angle of repose	SD	Flowability	SD	CI	HR
[g]	[%]**	[°]		[s/50 g]		[%]	
1.0	**4,2**	**NA**	**NA**	**45.31**	**0.81**	**15.29**	**1.18**
1.5	6,3	NA	NA	24.81	3.31	16.25	1.19
2.0	8,3	NA	NA	24.45	2.63	17.95	1.22

* Sample with most suitable properties is written **in bold**. ** In relation to the coating material. NA = not available.

Table 7. Flow properties of Fujicalin® and PG mixtures.

Amount of PG		Angle of repose	SD	Flowability	SD	CI	HR
[g]	[%]**	[°]		[s/50 g]		[%]	
10	**25.0**	**29.70**	**2.97**	**1.03**	**0.09**	**8.24**	**1.09**
11	27.5	27.30	1.21	0.95	0.05	10.23	1.11
12	30.0	32.60	1.39	1.10	0.07	10.59	1.12

* Sample with most suitable properties is written **in bold**. ** In relation to the coating material.

Table 8. Flow properties of Avicel® PH 101 and PG mixtures.

Amount of PG		Angle of repose	SD	Flowability	SD	CI	HR
[g]	[%]**	[°]		[s/50 g]		[%]	
1	2	35.53	1.68	7.46	0.41	21.96	1.28
2	4	37.83	0.96	5.64	3.26	18.67	1.23
3	6	35.45	0.92	3.07	0.12	18.18	1.22
4	8	36.97	1.31	3.07	0.34	16.22	1.19
5	10	34.80	6.70	3.08	0.25	15.79	1.19
6	**12**	**31.37**	**3.23**	**3.63**	**0.52**	**17.72**	**1.22**
7	14	35.25	1.53	4.95	0.67	17.02	1.21
8	16	40.10	0.69	6.03	0.40	16.47	1.20

* Sample with most suitable properties is written **in bold**. ** In relation to the carrier material.

The flowable liquid retention potential (Φ-value) of Fujicalin® mixed with PG was calculated as the ratio of amount of liquid vehicle (10 g) and weight of carrier (40 g) and was equal to 0.25 (Fig. 3).

Mixture of Avicel® PH 101 with propylene glycol

From Figure 4 it is obvious that adding of propylene glycol to Avicel® PH 101 initially decreased the values of angle of slide. Mixtures containing 3-6 g of PG revealed similar values of angle of slide, i.e., about 35.00°. Subsequent adding of propylene glycol increased angle of slide up to 48.67 ± 1.53° (mixture with 8 g of PG), which could be explained by the oversaturation of microcrystalline cellulose with propylene glycol. The value closest to 33° had the mixture containing 6 g of sorbed PG (34.83 ± 0.29°). The angle of repose (31.37 ± 3.23°) and flowability (3.63 ± 0.52 s/50 g) of this liquisolid blend referred to a good character of flow and its values of CI (17.72%) and HR (1.22) corresponded to fair flow properties (34).

Mixing Avicel® PH 101 with an increasing amount of PG implied that adding of a liquid vehicle initially had a negative effect on mixtures' angle of repose. The angle of repose values (Table 8) increased after adding PG up to 36.97 ± 1.31° (blend containing 4 g of PG) and then, after further adding of PG decreased to 31.37 ± 3.23° (6 g of PG). However, subsequent adding of PG increased angle of repose up to 40.10 ± 0.69° again (8 g of PG). The final deterioration of flow properties could have been caused by the oversaturation of carrier particles with PG.

Evaluation of flowability implied similar phenomenon as the angle of repose. Initially, the measured values decreased and then after adding more propylene glycol increased again. The lowest value of flowability (3.07 ± 0.34 s/50 g) showed the liquisolid powder containing 4 g of PG.

Compressibility index and Hausner ratio implied the same tendency as flowability and angle of repose. Their values corresponded to powders with fair/passable flow properties (34).

The flowable liquid retention potential (Φ-value) for Avicel® PH 101/PG admixture was calculated as the ratio of amount of liquid vehicle (50 g) and weight of carrier (6 g) and is equal to 0.12 (Fig. 3). This experimentally measured Φ-value is almost similar to those presented in scientific literature for

Avicel® PH 101 (0.16) (42, 45) and Avicel® PH 102 (0.16) (33, 43).

CONCLUSION

In the technique of liquisolid systems formulation, carrier and coating materials play dominant roles in an effort to obtain dry forms of powder from a drug in liquid state, which are suitable for further processing. Previously, it was observed that a high specific surface area and adsorption capacity of carriers and coating materials allowed incorporation of a greater amount of liquid. The evaluation of flowable liquid retention potential should constitute the main parameter when selecting the most suitable carrier/coating material for formulation of liquisolid systems. From the obtained results it could be concluded that 1 g of Neusilin® US2, Neusilin® UFL2, Neusilin® NS2N, Aerosil® 200, Fujicalin® and Avicel® PH 101 can retain 1.00, 0.97, 0.54, 0.04, 0.25 and 0.12 g of propylene glycol, respectively, while maintaining suitable flowing properties for further processing. Experimentally measured values of flowable liquid retention potential implied that there are available carriers with greater absorption capacity in comparison to the most commonly used microcrystalline cellulose. Magnesium aluminometasilicates (Neusilins®) promised a high potential as carriers and coating materials in the preparation of liquisolid systems.

REFERENCES

1. Javadzadeh Y., Siahi M.R., Asnaashari S., Nokhodchi A.: Acta Pharm. 57, 99 (2007).
2. Tiong N., Elkordy A A.: Eur. J. Pharm. Biopharm. 73, 373 (2009).
3. Hentzschel C M., Sakmann A., Leopold C.S.: Drug. Dev. Ind. Pharm. 37, 1200 (2011).
4. Karmarkar A.B., Gonjari I.D., Hosmani A.H.: Expert Opin. Drug. Deliv. 7, 1227 (2010).
5. Kavitha K., Lova Raju K.N.S., Ganesh N.S., Ramesh B.: Der Pharmacia Lettre 3, 71 (2011).
6. Javadzadeh Y., Jafari-Navimipour B., Nokhodchi A.: Int. J. Pharm. 341, 26 (2007).
7. Kulkarni A.S., Aloorkar N.H., Mane M.S., Gaja J.B.: Int. J. Pharm. Sci. Nanotechnol. 3, 7950 (2010).
8. Gavali S.M., Pacharane S.S., Sankpal S.V., Jadhav K.R., Kadam V.J.: Int. J. Res. Pharm. Chem. 1, 705 (2011).
9. Nokhodchi A., Hentzschel C.M., Leopold C.S.: Expert Opin. Drug Deliv. 8, 191 (2011).
10. Gubbi S., Jarag R.: Res. J. Pharm. Technol. 2, 382 (2009).
11. Khanfar M., Sheikh S.M., Hawari R.: Pharm. Dev. Technol. 18, 417 (2013).
12. Elkhodairy A.K., Samy M.W.: Lett. Drug Des. Discov. 9, 336 (2012).
13. Panda A., Biyani D. M.: Am. J. Pharmtech. Res. 3, 686 (2013).
14. Chella N., Shastri N., Tadikonda R.R.: Acta Pharm. Sin. B 2, 502 (2012).
15. Rowe R.C., Sheskey P.J., Owen S.C.: Handbook of Pharmaceutical Excipients, Pharmaceutical Press, London 2006.
16. Javadzadeh Y., Shariati H., Movahhed-Danesh E., Nokhodchi A.: Drug. Dev. Ind. Pharm. 35, 243 (2009).
17. Fuji Chemical Industry Co., Ltd.: http://www.harke.com/fileadmin/images/pharma/Broschueren/Fuji_Fujicalin_Brochure_SEP2011.pdf (accessed 15.1.2014).
18. Fuji Chemical Industry Co., Ltd.: http://www.neusilin.com (accessed 15.1.2014).
19. Hentzschel C. M., Sakmann A., Leopold C.S.: Pharm. Dev. Technol. 17, 649 (2012).
20. Fuji Chemical Industry Co., Ltd.: http://www.harke.com/fileadmin/images/pharma/Broschueren/Fuji_Neusilin.pdf (accessed 20.1.2014).
21. Taniguchi H.: EP 2540174 A1, 2013.
22. Krupa A., Majda D., Jachowicz R., Mozgawa W.: Thermochim. Acta 509, 12 (2010).
23. Sander C., Holm P.: AAPS PharmSciTech 10, 1388 (2009).
24. Hentzschel C.M., Alnaief M., Smirnova I., Sakmann A., Leopold C.S.: Eur. J. Pharm. Biopharm. 80, 130 (2011).
25. Khanfar M., Fares M.M., Salem M.S., Qandil A.M.: Micropor. Mesopor. Mat. 173, 22 (2013).
26. Vialpando M., Backhuijs F., Martens J.A., Van den Mooter G.: Eur. J. Pharm. Biopharm. 81, 190 (2012).
27. Wu Z., Jiang Y., Kim T., Lee K.: J. Control. Release 119, 215 (2007).
28. Ukmar T., Planinšek O.: Acta Pharm. 60, 373 (2010).
29. Vallet-Regi M., Ramila A., del Rea R.P., Pérez-Pariente J.: Chem. Mater. 13, 308 (2001).
30. Zhu W., Wan L., Zhang C., Gao Y., Zheng X., Jiang T., Wang S.: Mater. Sci. Eng. C. Mater. Biol. Appl. 34, 78 (2014).
31. Chen B., Quan G., Wang Z., Chen J., Wu L., Xu Y., Li G., Wu C.: Powder Technol. 240, 48 (2013).
32. Karmarkar A.B., Gonjari I.D., Hosmani A.H., Dhabale P.N., Bhise S.B.: Int. J. Health. Res. 2, 45 (2009).

33. Spireas S.S., Jarowski C.I., Rohera B.D.: Pharm. Res. 9, 1351 (1992).
34. European Pharmacopoeia 8.0.: http://online6.edqm.eu/ep800 (accessed 1.2.2014)
35. Elkordy A.A., Essa E.A., Dhuppad S., Jammiqumpula P.: Int. J. Pharm. 434, 122 (2012).
36. Elkordy A.A., Tan X.N., Essa E.A.: Eur. J. Pharm. Biopharm. 83, 203 (2013).
37. Bolhuis G.K., Zuurman K.: Drug Dev. Ind. Pharm. 21, 2057 (1995).
38. Takano K., Nishii K., Mukoyama A., Iwadate Y., Kamiya H., Horio M.: Powder Technol. 122, 212 (2002).
39. Nada A.H., Graf E.: Eur. J. Pharm. Biopharm. 46, 347 (1998).
40. Shah C.V., Patel H.K., Shah V.H., Upadhyay U.M.: Int. J. Pharm. Sci. Res. 3, 2741 (2012).
41. Hersh M., Lentine C.V.: US 4620974 A, 1985.
42. Kaur M., Bala R., Arora S.: Int. Res. J. Pharm. 4, 156 (2013).
43. Sathali A.A.H., Deepa C.: Int. J. Res. Pharm. Sci. 4, 238 (2013).
44. Zhou Q., Denman J.A., Gengenbach T., Das S., Qu L., Zhang H., Larson I. et al.: J. Pharm. Sci. 100, 3421 (2011).
45. Khanfar M., Salem M.S., Kaddour F.: Pharm. Dev. Technol. 19, 103 (2014).

Received: 19. 03. 2014